REMARKS

At the outset applicants wish to emphasize a subtle but important fact regarding semipermeable synthetic membranes. Specifically, applicants respectfully submit that the functional characteristics of such membranes are related to not only the materials comprising the membrane but are also highly influenced by the manner in which they are made. This is due in part to the fact that pore size and distribution of such pores within a membrane is influenced by how the membrane was formed. Numerous parameters (besides altering the composition of the reagents) can be varied during synthesis that will impact the pore size and distribution/number of pores. Such parameters include for example, varying the temperature of the nozzle, polymer solution, center fluid etc., varying the construction of the spinning nozzle and the spinning shaft, optionally spinning through a gap of air prior to entering the liquid bath, etc. In this regard, applicants have surprisingly discovered that raising the temperature (in the range of about 30° to about 80° C) of the spinning nozzle, the polymer solution and center fluid during the spinning process will produce a more open-pored membrane than is achieved using a standard methodology. This more open pore structure, not previously achieved by prior art methods, is indicated by the high sieving coefficients obtained for compounds having relatively large molecular weights (e.g., 26 kD and higher).

Measuring the sieving coefficient of a membrane is one manner, accepted by those skilled in the art, of characterizing the structure of a given synthetic semipermeable membrane (see Encyclopedia of Surface and Colloid Science, Volume 2, P. Somasundaran Ed.p.6397 (June 15, 2006). Sieving coefficients are factually and mathematically linked to the pore structure of a membrane and as such they define the averaged combined structure of a membrane. Accordingly, applicants respectfully submit that the claim limitations regarding sieving coefficients are limitations that define the structure of a membrane in a manner consistent with this field and accepted by those skilled in the art.

The claims are amended herein to more particularly define specific embodiments of the present invention and to further distinguish the claimed invention from the membranes disclosed in the prior art. More particularly, claim 1 has been amended to further recite that the claimed membranes have a sieving coefficient of 0.9 to 1.0 for a relative large molecular weight protein (IL-6; MW about 26 kD). In addition claim 14 has been placed in independent form reciting the sieving coefficient limitations of claim 1 as well as specifying the number and distribution of the

pores in the outer layer of the claimed membrane. Support for the amendments to claims 1 and 14 is found is found throughout the specification, including for example in numbered paragraph [0049]. New claims 35 and 36 have been added to claim a membrane formed using applicants' unique processing steps. Support for that amendment is found throughout the specification including for example in numbered paragraph [0054] and [0056].

Claim 34 stands rejected under 35 USC 112, first paragraph for lack of written description. Applicants respectfully traverse this rejection, but to advance the prosecution of this application, applicants have canceled claim 24 rendering the rejection moot.

Claims 1-3-7, 9-10, 12-13 and 34 stand rejected under 35 USC 102(e) as anticipated by, or in the alternative under 35 USC 103(a) as obvious, over the teachings of Kim et al in view of Gorsuch et al. Applicants respectfully traverse this rejection.

The Examiner contends that Kim discloses a hollow fiber membrane "with the same preferred structure as contained in applicant's claims/specification". Applicants respectfully traverse such a statement, noting in fact that applicants' membranes have sieving coefficients that are distinct from those of Kim's disclosed membranes. Furthermore, applicants respectfully submit that the Examiner is overstating the teaching of Gorsuch when using that reference to support the premise that "size exclusion limits can be easily manipulated based on the test methods used to determine the size exclusions limits". As stated above and noted by the Examiner there are "a multitude of possible structural and operational limitations" that can impact the pore size and pore distribution on a membrane.

Applicants respectfully submit that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). There are many parameters that can be varied during the process of sythesizing semipermeable membranes, and while the art suggests that altering certain parameters may impact the structure of the resulting membrane, there is no guidance of how to prepare the open pore structured membranes of the present invention. Simply stated, until applicants' invention, no one has disclosed a synthetic membrane having the combination of structure elements of applicants' claimed membrane as defined by the claimed sieving coefficients for compounds having a

molecular weight of 26-45 KD. Applicant were the first to spin polymer solutions at elevated temperatures (relative to standard protocols) and surprisingly found that such a process produced membranes having such an open-pored structure with a molecular weight exclusion limit of about 200,000 Daltons. In an area of technology shown to be highly unpredictable in process values, the discovery of values not in any way suggested by the prior art is more likely to be unobvious than obvious within the meaning of 35 USC 103. *In re Sebek*, 465 F.2d 904, 175 USPQ 93, 95 (CCPA 1972). Applicants' claimed compositions are the result of a unique synthesis protocol that was not taught or suggested by the prior art.

Applicants also respectfully submit that the Examiner has overstated the teachings of the primary Kim reference regarding their membrane's ability to allow passage of molecules having a molecular weight of up to 45 kD. The Examiner states that Kim discloses an asymmetric hollow fiber membrane which "allows passage of molecules having a molecular weight of up to 45 kD with a sieving coefficient of 0.1- 1.0 in the presence of whole blood", making reference to Table 1 of Kim. However, applicants note that a molecular weight cut-off is generally defined as the minimal molecular weight of a globular protein which is retained by a membrane. Table 1 of Kim states the membrane has a cut-off (MW x 10^{-3}) of 40± 5, which means compounds having a molecular weight ranging from 35,000 to 45,000 will be prevented from crossing the membrane.

Accordingly, the membrane described by Kim et al. will certainly not allow for the passage of molecules having a MW of 45 kD. On the contrary, the membrane according to the present invention and as claimed in claim 1, allows the passage of molecules having a molecular weight of up to 45 kD with a sieving coefficient (SC) of 0.1-1.0. Thus at least 10% and up to 100% of 45 kD molecule may pass through the membrane, whereas the membrane of Kim et al. win retain all of such molecules.

Closer inspection of the data presented in Table 1 of Kim reveals further evidence of the structural differences between the membrane of Kim and the presently claimed membrane. In particular, Table 1 of Kim et al. discloses the sieving coefficient for alpha-1-microglobulin is, on average, 0.20 for the membrane disclosed therein. This sieving coefficient value corresponds to a passage of only 20% of said molecules through the membrane.

The sieving coefficient has not been determined for the presently claim membrane with regards to alpha-1-microglobulin. However, IL-6, has a MW ranging from about 21 to about 29 kD (due to extensive and variable phosphorylation and glycosylation). Thus IL-6 has an average molecular weight (about 26 kD) that is in the same range as alpha-1-microglobulin (MW ranging

from about 25-33 kD). IL-6 has a SC of 0.95 for the membrane of the present invention, corresponding to a passage of 95% of the molecules through the membrane (see Table 1 of the present application). Accordingly, the sieving coefficient for these two similar compounds is dramatically different for the respective two membranes 0.20 vs. 0.95, providing another indication that the structure of the two membranes is different.

In addition, the passage of albumin has been determined for both membranes. As disclosed in Kim et al., albumin has a sieving coefficient of 0.004-0.005 for their membrane. As shown in the previously submitted Declaration of Hermann Goehl (submitted on August 20, 2010), the membrane of the present invention shows a sieving coefficient for albumin of up to 0.1 (10%, see Table 1, HCO 1100), but at least 0.011 (see Table on page 16 of the specification). Thus membranes of the present invention have sieving coefficients which are 10 to 100 times higher than the sieving coefficients shown for albumin in Table 1 of Kim et al.

It is generally accepted in the art that sieving coefficients are one of the most reliable parameters in defining the physical characteristics of a membrane (see Encyclopedia of Surface and Colloid Science, Volume 2, P. Somasundaran Ed.p.6397 (June 15, 2006). Sieving coefficients are determined according to a standard protocol, which is adhered to by all persons with skill in the art producing membranes for use in medical devices. Thus sieving coefficients provide a reliable characterization of the physical structure of membranes. Accordingly, applicants respectfully submit that the membranes disclosed in Kim et al are clearly different than the membranes disclosed and claimed in the present invention. Furthermore, the cited art references are devoid of any teaching or suggestion of how to modify the prior art processes to produce the presently claimed open-pored structures of the present invention.

Gorsuch has disclosed the sieving coefficients for several different types of membranes, more particularly between high-flux membranes (left curve) and plasma separation membranes (right curve) in Figure 7. These membranes are fundamentally different based on their composition, the processes used to prepare then and their resulting physical structure. Accordingly, Gorsuch fails to provide any guidance for synthesizing a membrane of applicants' composition and having the claimed open pore structure as defined by the enumerated sieving coefficients and pore sizes and distributions. Figure 7 of Gorsuch simply shows that different types of membranes produce different curves for sieving coefficients. Thus Gorsuch provides no guidance to one of ordinary skill in the art of how to manipulate the process of preparing a synthetic membrane to produce the opened structured membrane of the present invention absent

undue experimentation. Thus Gorsuch fail to supplement the inadequacies of the Kim et al teaching with regards to the claimed invention.

Accordingly, applicants respectfully submit the combined teachings of Kim et al and Gorsuch fail to teach or suggest the claimed invention. Applicants therfore respectfully request the withdrawal of the rejection of claims 1-3-7, 9-10, 12-13 and 34 as being anticipated by or in the alternative obvious over the teachings of Kim et al in view of Gorsuch et al.

Claim 2 stands rejected under 35 USC 103(a) as obvious over the teachings of Kim et al in view of Deppisch. Applicants respectfully traverse this rejection.

Claim 2 depends from claim 1 and therefore encompasses all the elementsrecited in claim 1. Deppisch fails to provide any guidance of how to alter prior art processes to produce a membrane have the overall structural elements of applicants' claimed membrane as defined by the recited sieving coefficients. As noted above, sieving coeffients are an art accepted measurement for defining semipermeable membrane structure.

Applicants have discovered that by proceeding contrary to accepted teaching and using elevated temperatures during the spinning step they can produce a membrane have properties not previously described. The resultant membranes have open pored structure that allows for high sieving coefficients for compounds having a molecular weigh of 26 KD while retaining higher molecular weigh compounds such as albumin. Claim 2 is believed patentable over the teachings of Kim et al in view of Deppisch and applicants respectfully request the withdrawal of that rejection.

Claims 11, 14-15, 29-31 and 33 stand rejected under 35 USC 103(a) as obvious over the teachings of Kim et al in view of Buck et al as evidenced by Gorsuch et al. and Kagawa et al. Applicants respectfully traverse this rejection.

The deficiencies of the Kim and Gorsuch teachings regarding the present invention have been discussed above and the secondary references fail to supplement the inadequacies of those teachings. In particular, the cited prior art fails to teach or suggest a method that will produce a membrane of applicant's composition that has its overall structure as defined by applicants uniquely held sieving coefficients. The Examiner has cited Buck for disclosing membranes having a separation layer that contains pore channels with a pore size of 20-40 nm. However, this is only one component structure of applicants' membrane and applicants respectfully dispute

the Examiner's contention that those skilled in the art know how to manipulate synthetic protocols to easily input desired physical properties into the final product.

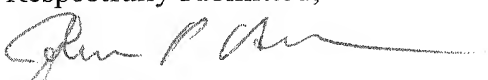
Applicants use sieving coefficients to define the structure of their membranes as it relates to the complete structure of the formed membrane and takes into account that the claimed membrane has pore sizes in the separation layer of 15-60 nm (claim 11) in combination with pores on the outer surface having sizes in the range of 0.5-3 um and a distribution of such pores is in the range of 20,00 to 100,000 pores/mm^2 (claim 14) as well as other structural elements of the membrane. Applicants have disclosed a unique method of synthesizing synthetic membranes using steps (particularly, using an elevated spinning temperature) to produce a membrane having a unique combination of physical structures that are defined by the sieving coefficient.

The mere fact that a reference discloses a membrane that has one or two of the physical structures of the presently claimed membrane does not teach how to plug that value into other known membranes. The combined teaching of all the cited references simply fail to teach applicants unique method of preparing a membrane that has applicant's total combined structure as defined by the recited the sieving coefficient. Applicants respectfully submit that while one may "envision" that such properties could be incorporated into a membrane, the references fail to enable one how to actually do so to create the unique combination of physical structures present in applicant's claimed invention. Contrary to the Examiner's statement regarding "routine manipulation" to "optimize" workable ranges, there is simply no teaching or suggestion that raising the spinning temperature to 30 ° C to 80° C would produce membranes of the claimed invention. Applicants respectfully submit that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

Applicants respectfully submit that the claimed invention has been narrowly tailored to claim the unique structure that results from applicants novel method of synthesis. The prior art for all its combined teaching fails to teach how to make the unique membrane structure as claimed herein as defined in part by the novel sieving coefficient values. Claims 11, 14-15, 29-31 and 33 are believed to be patentably distinct over the teachings of Kim et al in view of Buck et al as evidenced by Gorsuch et al. and Kagawa et al. and applicants respectfully request the withdrawal of the rejection over those references.

The claimed invention, as amended herein, is believed to be patentably distinct over the cited prior art and applicants respectfully request the withdrawal of the rejections and passage of the application to allowance. If the Examiner has any questions or comments such that a conversation would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,



John P. Breen
Registration No. 38,833
Attorney for Applicants

(317) 261-7940
Indianapolis, Indiana 46204